REMARKS

Claim 9 is pending in the instant application. Claim 9 has been rejected. Claim 9 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claim 9 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Moyer et al. ((Aug. 1999) *Am. J. Physiol.* 277(2 Pt 2):F271-6) in view of Riordan et al. (WO 01/03722), Cormack et al. ((1996) *Gene* 173:33-38), McCray et al. (U.S. 6,855,549), Chou et al. (1991) *J. Biol. Chem.* 266:24471-24476), and Dalemans et al. (U.S. 6,136,594). The Examiner suggests that Moyer et al. teach a method of measuring the effect of butyrate on the expression of a CFTR-GFP. It is suggested that because the specification does not define EGFP, this claim limitation is met by Moyer et al. The Examiner acknowledges that Moyer et al. do not teach the mutant human ΔF508 CFTR protein, the method of using proximal human CFTR promoter region or the specific species of EGFP reporter gene. It is suggested, however, that Riordan et al. teach a method for increasing the amount of CFTR on cell surface of a cell by contacting with an agent, wherein the cells express ΔF508 CFTR protein. It is further suggested that Cormack et al. teach the cloning of GFP mutants, which fluoresce more intensely than wild-type GFP, wherein McCray et al. teach the cumulative of Cormack et al. of an EGFP reporter construct with the CFTR. In addition, it is suggested that Chou et al. teach the transcription regulatory

elements of CFTR gene and that one was a proximal positive element delimited by the 5′ deletion constructs -226 base pairs upstream of the transcription start site. Furthermore, Dalemans et al. are suggested to teach a vector for expression in a cell comprising the human CFTR gene which is under control of the endogenous human CFTR promoter, wherein it is suggested that Dalemans et al. teach that ΔF508 is a mutant allele which is expressed at low levels and associated with disease of CF.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Moyer et al. to substitute ΔF508 cDNA taught by Riordan et al. with the motivation of increasing the level of ΔF508 or CFTR in treatment of cystic fibrosis. It is further asserted that it would have been obvious to modify the method of Moyer et al. and Riordan et al. to use the proximal human CFTR promoter region of Chou et al. because Chou et al. teaches that the promoter of CFTR can be used to obtain insights into the mechanisms governing the regulation of CFTR expression, wherein Dalemans et al. provide further motivation to express CFTR genes and use the endogenous promoter. The Examiner suggests that were Applicants to argue that the term "EGFP" is not encompassed by the teachings of Moyer et al. GFP, it would have been obvious to modify the teachings of Moyer et al. to use the modified GFP of Cormack et al. or EGFP of McCray et al. because Cormack et al. teach that optimized GFP has a greatly increased fluorescence intensity, making the mutants useful for a number of applications.

Applicants respectfully disagree with this rejection. Applicants have appreciated that the claimed construct expresses

the ΔF508 CFTR mutant protein and also provides a detectable readout for identifying agents which increase the expression, activity or trafficking of ΔF508 CFTR mutant protein. In particular, Applicants have demonstrated that anthracycline drugs such as doxorubicin unexpectedly increase the functional expression of CFTR and ΔF508 CFTR at the cell surface. See pages 9 and 10. In this regard, the specification teaches that anthracycline drugs and derivatives or metabolites thereof are an example of one class of pharmacological agents which can be used to increase functional cell surface protein expression of a mutant CFTR so that the phenotype of cystic fibrosis caused by this mutant is reversed. See page 10, lines 25-31. Accordingly, in an earnest effort to highlight the class of drugs which can be screened in accordance with the instant method and distinguish the present invention from the teachings of the cite documents, Applicants have amended claim 9 to indicate that the agent being screened is an anthracycline. Support for this amendment is found at pages 9 and 10 of the specification, and in particular at page 10 (lines 15-35), which discusses the use anthracyclines in the methods of the invention and provides specific examples of this class of agents, *i.e.*, doxorubicin, idarubicin, anthracenedione derivatives such as mitoxantrone and metabolites such as doxorubicinal.

Under 35 U.S.C. §103, the factual inquiry into obviousness requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4)

secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

In so far as the combined teachings of the cited documents fail to teach or suggest screening this class of agents, the cited documents cannot be held to make the present invention obvious. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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